II. REMARKS

Formal Matters

Claims 1, 3, 5, 7, 14, 15, and 20-23 are pending after entry of the amendments set forth herein.

Claims 1, 3, 5, 7, 14, 15, and 20-22 were examined and were rejected. Claims 9-13 and 16-19 were withdrawn from consideration.

Claims 9-13 and 16-19 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claim 23 is added. Support for new claim 23 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: paragraph 0038; and paragraph 0050. Accordingly, no new matter is added by this new claim.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner T.N. Ton and Examiner D. Crouch for the courtesy of a telephonic interview which took place on February 9, 2005, and which was attended by Examiners Ton and Crouch, inventor Dr. Karl Weisgraber, and Applicants' representative Paula A. Borden.

During the interview, the rejection of claims 1, 3, 5, 7, 14, 15, and 20-22 under 35 U.S.C.§ 112, first paragraph, was discussed. During the interview, the new matter rejection was discussed. It is the understanding of the undersigned Applicants' representative that the new matter rejection has been withdrawn in view of remarks made during the interview.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 3, 5, 7, 14, 15, and 20-22 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the enablement requirement.

Comments regarding the enablement requirement of 35 U.S.C.§112, first paragraph

The enablement requirement of 35 U.S.C.§112, first paragraph, requires that the specification disclose at least one method for making and using the claimed invention that bears a reasonable correlation to the scope of the claim. Where a composition is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of the claim is sufficient.

Claims under examination

Claims 1 and 3 are drawn to a gene-targeted mouse; claims 5, 7, and 20-22 are drawn to a cell isolated from the gene-targeted mouse; and claims 14 and 15 are drawn to a method of identifying an agent that reduces a phenomenon associated with Alzheimer's disease (AD), using the gene-targeted mouse.

ApoE4 is known to be associated with various pathological conditions.

As explained by Dr. Weisgraber during the February 9, 2005 telephonic interview, apoE4 is a known risk factor for several neurodegenerative disorders, including AD, and for cardiovascular disease. This fact is illustrated by the following references. Abstracts of these references are provided herewith as Exhibits 2-8.

1. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. (1993) Apolipoprotein E: High-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc. Natl. Acad. Sci. USA* **90**: 1977–1981.
2. Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD. (1993) Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**: 1467–1472.
3. Eichner JE, Kuller LH, Orchard TJ, Grandits GA, McCallum LM, Ferrell RE, Neaton JD. (1993) Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. *Am. J. Cardiol.* **71**: 160–165.
4. Mayeux R, Ottman R, Maestre G, Ngai C, Tang M-X, Ginsberg H, Chun M, Tycko B, Shelanski M. (1995) Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease. *Neurology* **45**: 555–557.
5. Fazekas F, Strasser-Fuchs S, Schmidt H, Enzinger C, Ropele S, Lechner A, Flooh E, Schmidt R, Hartung H-P. (2000) Apolipoprotein E genotype related differences in brain lesions of multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* **69**: 25–28.
6. Drory VE, Birnbaum M, Korczyn AD, Chapman J. (2001) Association of *APOE* ε4 allele with survival in amyotrophic lateral sclerosis. *J. Neurol. Sci.* **190**: 17–20.
7. Roses AD. (1998) Apolipoprotein E and Alzheimer's disease. The tip of the susceptibility iceberg. *Ann. N.Y. Acad. Sci.*

855: 738–743.

The instant specification provides ample enablement for use of a gene-targeted mouse, or a cell isolated therefrom, as recited.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1), a cell isolated from such an animal, or a recombinant apoE polypeptide made by such an animal or a cell, is useful for carrying out drug screening assays to identifying agents that reduce apoE4 domain interaction. Specification, page 29, paragraph 00108; page 21, paragraph 0082; and page 22, paragraph 0083; and paragraph 00196. The specification goes on to describe in detail how such drug screening assays would be performed. Specification, page 29, paragraph 00108 to page 44, paragraph 00150.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with an apoE4-related neurological disorder. Specification, page 30, paragraph 00108; paragraph 00109; paragraph 0028; and paragraph 00196. The specification states that apoE-related neurological disorders include AD, poor outcome following a stroke, poor outcome following head injury, and cerebral ischemia. Specification, paragraph 0050. The specification states that apoE-related neurological disorders can be assessed by pathological studies, including an assessment of neurodegeneration. Specification, pages 39-40, paragraphs 00135-00136. The specification states that neuronal damage is assessed using well-known assays, including neuronal damage associated with traumatic brain injury and traumatic ischemic insult to the brain. Specification, pages 42-44, paragraphs 00145-00147.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with AD. Specification, page 8, paragraph 0029. The specification states that phenomena associated with AD include neuropathological developments. Specification, paragraph 0046. Such neuropathological developments include neurodegeneration. Specification, paragraph 00127; and paragraph 00128.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce cholesterol levels in an individual, and to treat hyperlipidemia in an individual Specification, page 8, paragraph 0030; page 44, paragraphs 00148-00150. The instant specification states that phenomena associated with apoE4-associated disorders include high serum cholesterol levels. Specification, page 12, paragraph 0050.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce the risk of coronary artery disease and cardiovascular disorders. Specification, page 8, paragraph 0031; page 29, paragraph 00108; page 44, paragraphs 00148-00150; and paragraph 00196. The specification states that apoE-related disorders associated with high serum lipid levels include atherosclerosis and coronary artery disease. Specification, page 12, paragraph 0050. The specification states that the effect of a test agent on apoE4-related cardiovascular disorders can be assessed by pathological studies. Specification, page 40, paragraph 00137.

The instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1), a cell isolated from such an animal, or a recombinant apoE polypeptide made by such an animal or a cell, is useful for identifying an agent that disrupts interaction of apoE with lower density lipoproteins. Specification, page 8, paragraph 0032; page 37-38, paragraphs 00131 and 00132.

The instant specification provides data showing that a gene-targeted mouse as claimed produces a modified apoE protein having Arg at a position equivalent to Arg-61 in human apoE4, and that the Arg-61 apoE produced by the gene-targeted mouse exhibits preferential binding to lower density lipoproteins. Specification, Example 1, e.g., paragraphs 00191, 00194, and 00195. These data demonstrate that the Arg-61 apoE protein produced by the gene-targeted mouse exhibits domain interaction, is a model for human apoE4 domain interaction, and is therefore useful for identifying agents that interfere with the domain interaction, which agents are useful to treat disorders such as cardiovascular diseases and neurodegenerative diseases associated with human apoE4. Specification, paragraph 00196.

In addition, a Declaration of Dr. Karl Weisgraber ("Weisgraber Declaration"), provided herewith as Exhibit 1, demonstrates that a gene-targeted mouse as claimed exhibits a degree of neurodegeneration that is greater than a control mouse. The data in the Weisgraber Declaration provide further support for the fact that a gene-targeted mouse as claimed is useful for identifying agents that treat apoE4-related neurodegeneration.

Thus, the instant specification enables use of a claimed gene-targeted mouse, and of a cell isolated from a claimed gene-targeted mouse, in screening for agents that treat a variety of disorders. Accordingly, claims 1, 3, 5, 7, and 20-22 are in compliance with the enablement requirement of 35 U.S.C.§112, first paragraph.

The instant specification provides ample enablement for a method of identifying an agent that reduces a phenomenon associated with AD.

As discussed above, the instant specification states that a subject gene-targeted animal (e.g., an animal as recited in claim 1) is useful for identifying agents that reduce a phenomenon associated with AD. Specification, page 8, paragraph 0029; and paragraph 00196. The specification states that phenomena associated with AD include neuropathological developments. Specification, paragraph 0046. Such neuropathological developments include neurodegeneration. Specification, paragraph 00127; and paragraph 00128.

Furthermore, as discussed above, the Weisgraber Declaration demonstrates that a gene-targeted mouse as claimed exhibits a degree of neurodegeneration that is greater than a control mouse. The data in the Weisgraber Declaration provide further support for the fact that a gene-targeted mouse as claimed is useful for identifying agents that treat apoE4-related neurodegeneration such as AD.

Thus, the instant specification enables use of a claimed gene-targeted mouse in a method of identifying agents that reduce a phenomenon associated with AD. Accordingly, claims 14 and 15 are in compliance with the enablement requirement of 35 U.S.C.§112, first paragraph.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1, 3, 5, 7, 14, 15, and 20-22 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-222.

Respectfully submitted,
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Date: Feb. 25 2005

By: _____
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